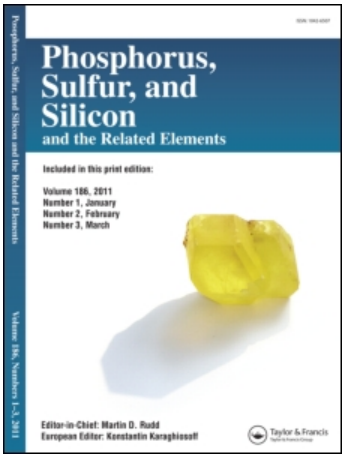

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Convenient Synthesis of Some 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines Bearing 3-Methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}moiety as Possible Antimicrobial Activity

Mamdouh A. M. Taha[a]
[a] Chemistry Department, Faculty of Science, Faiyoum University, Faiyoum, Egypt

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Convenient Synthesis of Some 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines Bearing 3-Methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}moiety as Possible Antimicrobial Activity

Mamdouh A. M. Taha
Chemistry Department, Faculty of Science, Faiyoum University, Faiyoum, Egypt

*4-Amino-4H-3-methylthio{7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl}-1,2,4-triazole-5-thi-ol (**1**) was condensed with various substituted aromatic aldehydes or acid chlorides to yield a series of arylideneamines **2** or aroylamines **3**. These were easily cyclized to the corresponding 6-aryl-3-methylthio7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazoles (**4**) on treatment with palladium-on-charcoal or phosphorus oxychloride. Compounds **4** were also prepared directly via the reaction of **1** with aromatic carboxylic acids in the presence of phosphorus oxychloride. Cyclocondensation of **1** with a variety of two-carbon cyclizing reagents, namely chloroacetone, pyruvic acid, benzoylformic acid, and benzoin led to the formation of 3-methylthio{7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl}-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (**5**–**8**). Some of the newly synthesized compounds were tested for their antibacterial and antifungal activity against a variety of microorganisms.*

Keywords Antimicrobial activity; triazole; triazolotetrazole; triazolothiadiazoles; triazolothiadiazines

INTRODUCTION

A review[2] reveals that publications dealing with the synthesis of condensed 1,2,4-triazolo-heterocycles are associated with a wide range of diverse types of biological properties. A large number of triazolothiadiazoles and triazolothiadiazines have recently been reported to

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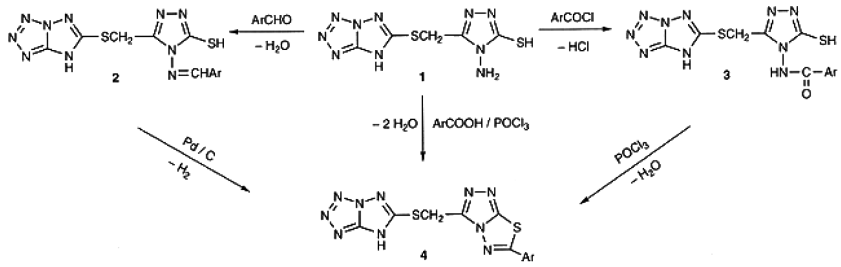
Address correspondence to Mamdouh A. M. Taha, Chemistry Department, Faculty of Science, Faiyoum University, Faiyoum 63514, Egypt. E-mail: mamdouhamtaha@yahoo.com

possess CNS depressant, antibacterial, antifungal, antitumor, anti-inflammatory, herbicidal, pesticidal, and insecticidal properties.[3–12]

Therefore, it was envisaged that chemical entities with both 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines, bearing 3-methylthio {7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl} linkage would result in compounds of interesting antimicrobial activity.

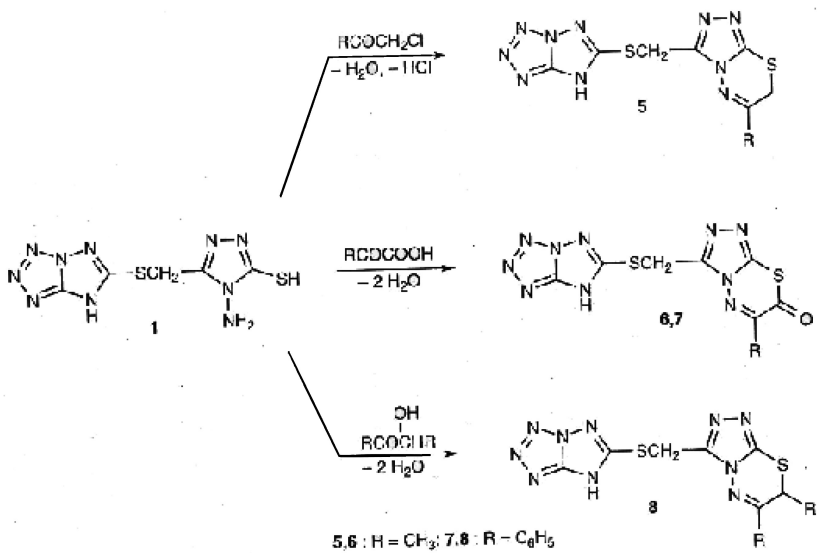
RESUTLS AND DISCUSSION

The syntheses of the title compounds were accomplished as shown in Schemes 1 and 2. The reaction of 4-amino-4H-3-methylthio{7H-1,2,4-triazolo[1,5-*d*] tetrazol-6-yl}-1,2,4-triazole-5-thiol[1] (**1**) with aromatic aldehydes gave the expected yellow arylideneamines (**2**) in excellent yields. Their ^{1}H NMR spectra revealed common characteristic signals assignable to the methylenic (—N=CH—) and aromatic protons. Their MS showed the expected molecular ion peaks in agreement with the assigned structures. Refluxing[13] compound **1** with aromatic acid chlorides afforded aroylamines **3**. All products showed the presence of an amide group (—N—C=O) through their absorption band in the IR spectra. The MS of the aroylamines **3** revealed the expected molecular ions, and their elemental analyses confirmed their formulas. The products **2** and **3** underwent cyclization into 6-aryl-3-methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **4**, when their refluxed with 5% palladium-on-charcoal in ethanol and phosphorus oxychloride, respectively. The formation of cyclized compounds **4** were confirmed on the basis of spectral studies. The IR spectrum of each product did not show any SH (2600–2545 cm^{-1}) and amide absorption band; only NH absorption was present (tria-



Ar: a = C_6H_5; b = $CH_3C_6H_4$ *(p)*; c = ClC_6H_4 *(p)*; d = $NO_2C_6H_4$ *(p)*

SCHEME 1



SCHEME 2

zolotetrazole). The ^{1}H NMR spectra of the cyclized products showed the disappearance of the signals assigned to methylenic and NH (aroylamino) protons in the spectra of the parent compounds **2** and **3**, respectively. The characteristic proton signal (3.82−3.45 ppm) of the SH group of the parent **2** and **3** was absent in ^{1}H NMR spectra of the cyclized products. Interestingly, compounds **4** can easily be obtained directly from **1** with aromatic carboxylic acids in the presence of phosphorus oxychloride. These products were identical in all aspects to that above described methods (m.p., mixed m.p., TLC, and IR). Recently, it has been also reported[3−5,13,14] that the same procedure by ring closure of aminothiols using carboxylic acids. The physical constants and spectral data of compounds (**2–4**) are listed in Tables I and II.

Furthermore, aminothiols can be considered[3,15] as key starting materials for the synthesis of diverse 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine compounds. Thus, the aminothiol **1** reacted in one-pot with two-carbon cyclizing reagents, namely chloroacetone, pyruvic acid, benzoylformic acid and benzoin, to construct 3-methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazo-6-yl}-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine derivatives (**5**−**8**), respectively. The elemental and spectroscopic data of these compounds are consistent with the assigned structures and are given in the Experimental section.

Antimicrobial Activities

Some of the prepared compounds were screened for their antimicrobial activity (determined in Extension Laboratory, Faculty of Agriculture, Alexandria University, Alexandria, Egypt) using *Staphylococcus aureus* (Gram- positive) and *Escherichia coli* (Gram-negative) bacteria, in addition to a *Candida albicans* (fungus) microorganisms. The activities of these compounds were used for the determination[16,17] of antibacterial and antifungal activity. Solutions of these compounds, ampicillin trihydrate and clotrimazole were dissolved in DMSO at concentration of 1600 mg/mL. The minimal inhibitory concentrations (MIC) were measured in mg/mL (Table III) at the end of the incubation period for 24 h to 48 h at 36°C. Controls for the DMSO microorganisms and media microorganisms were also undertaken. The results showed that compounds **3a** and **3c** exhibited activity comparable 25% of the ampicillin against *S. aureus*. While the effect of **3a** and **3c** were 50% of the ampicillin against *E. coli* , the activity of **3a** and both **2c** and **3c** were 50% and 25% against *C. albicans* comparable to clotrimazole, respectively. The remaining compounds showed lower activity than the reference standards (ampicillin, clotrimazole) against the test organisms. All these results are based on preliminary tests; more studies are to be conducted to get conclusive results.

CONCLUSION

Thiadiazole and thiadiazine derivatives in this article have been synthesized via the reaction of **1** with one/two-carbon cyclizing reagents and were identified by microanalyses and spectral data. Furthermore, some of the new synthesized compounds were screened for their antibacterial and antifungal activities.

EXPERIMENTAL

Melting points were taken in open capillary tubes in a MEL-TEMP II melting apparatus and are uncorrected. The purity of compounds was confirmed by thin layer chromatography using plates precoated with Silica Gel G (Merck: layer thickness 0.25 mm). All the spots were detected by exposition to iodine vapour for a few minutes. The infrared spectra (IR) were recorded on a Perkin-Elmer FT Paragon 1000 and Pye-Unicam SP-300 spectrometers in KBr (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded using a Varian Mercury VXR-3000 spectrometer using tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were recorded on a Shimadzu GCMS-Q 1000 EX mass spectrometer at

70eV. Microanalyses were performed by the Microanalytical Unit, Cairo University, Giza, Egypt.

General Procedure for the Preparation of 4-arylideneamino-3-methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-1,2,4-triazole-5-thiols (2a–d)

A mixture of compound **1**[1] (0.5 g, 1.85 mmol) and the appropriate aromatic aldehyde (0.2 g, 1.85 mmol) namely: benzaldehyde, *p*-tolualdehyde, *p*-chlorobenzaldehyde, and *p*-nitrobenzaldehyde in ethanol (20 mL) was refluxed for 30 min. The solvent was evaporated and the formed precipitate was filtered off and recrystallized from ethanol to yield yellow crystals. The physical constants and spectral data of compounds (**2a–d**) are given in Tables I and II.

TABLE I Physical Constants of Compounds (2–4)

Compound	Yield (%)	M.p. (°C)	Molecular formula	Analysis (%) Calcd. /Found C	H	N
2a	86	170–172	$C_{12}H_{10}N_{10}S_2$	40.22	2.79	39.11
				40.61	2.52	39.49
2b	84	180–182	$C_{13}H_{12}N_{10}S_2$	41.94	3.23	37.63
				42.32	3.48	38.12
2c	85	186–188	$C_{12}H_9ClN_{10}S_2$	36.69	2.29	35.67
				36.53	2.62	35.91
2d	88	190–192	$C_{12}H_9N_{11}O_2S_2$	35.73	2.23	38.21
				35.63	2.58	38.63
3a	65	184–186	$C_{12}H_{10}N_{10}OS_2$	38.50	2.67	37.43
				38.41	3.12	37.52
3b	71	189–190	$C_{13}H_{12}N_{10}OS_2$	40.21	3.09	36.08
				40.53	3.58	36.33
3c	75	196–198	$C_{12}H_9ClN_{10}OS_2$	35.25	2.20	34.27
				34.91	2.43	34.73
3d	74	200–202	$C_{12}H_9N_{11}O_3S_2$	34.37	2.15	36.75
				34.11	2.38	36.53
4a	76 (A), 54(B), 56(C)	190–191	$C_{12}H_8N_{10}S_2$	40.45	2.25	39.33
				40.88	2.11	39.18
4b	78(A), 59(B), 62(C)	195–196	$C_{13}H_{10}N_{10}S_2$	42.16	2.70	37.84
		210–211	$C_{12}H_7ClN_{10}S_2$	42.56	2.62	38.33
4c	77(A), 58(B), 61(C)			36.88	1.79	35.85
				37.21	2.23	35.48
4d	81(A), 61(B), 64(C)	218–219	$C_{12}H_7N_{11}O_2S_2$	35.91	1.75	38.40
				35.73	2.15	37.91

TABLE II Spectral Data of Compounds (2–4)

Compound	Spectral Data
2a	IR : ν = 3235 (NH), 2555 (SH) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.70 (s, 1H, NH), 8.30–7.52 (m, 5H, ArH), 7.33 (s, 1H, —N═CH), 4.20 (s, 2H, CH_2), 3.82 (s, 1H, SH) ppm. MS: *m/z* (%) = 359 (M^+ + 1, 17).
2b	IR : ν = 3200 (NH), 2570 (SH) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.60 (s, 1H, NH), 7.92–7.63 (m, 4H, ArH), 7.13 (s, 1H, —N═CH), 4.15 (s, 2H, CH_2), 3.75 (s, 1H, SH) 2.91 (s, 3H, CH_3) ppm. MS: *m/z* (%) = 372 (M^+ , 25).
2c	IR : ν = 3195 (NH), 2590 (SH) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 11.92 (s, 1H, NH), 8.22–7.66 (m, 4H, ArH), 7.22 (s, 1H, —N═CH), 4.12 (s, 2H, CH_2), 3.80 (s, 1H, SH) ppm. MS: *m/z* (%) = 392 (M^+ , 28).
2d	IR : ν = 3230 (NH), 2600 (SH) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.65 (s, 1H, NH), 8.22–7.52 (m, 5H, 4ArH + —N═CH), 4.15 (s, 2H, CH_2), 3.75 (s, 1H, SH) ppm.
3a	IR : ν = 3325 (NH), 2550 (SH) 1670 (NCO) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.62, 11.25 (2s, 1H each, 2NH), 8.20–7.28 (m, 5H, ArH), 4.15 (s, 2H, CH_2), 3.74 (s, 1H, SH) ppm. MS: *m/z* (%) = 374 (M^+ , 12).
3b	IR : ν = 3290 (NH), 2600 (SH) 1660 (NCO) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.51, 11.81 (2s, 1H each, 2NH), 8.15–7.62 (m, 4H, ArH), 4.22 (s, 2H, CH_2), 3.74(s, 1H, SH), 2.53(s, 3H, CH_3) ppm. MS: *m/z*(%) = 388 (M^+, 19).
3c	IR : ν = 3280 (NH), 2550 (SH) 1665 (NCO) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 11.91, 11.62 (2s, 1H each, 2NH), 8.24–7.14 (m, 4H, ArH), 4.18 (s, 2H, CH_2), 3.71 (s, 1H, SH) ppm. MS: *m/z* (%) = 408 (M^+ , 25).
3d	IR : ν = 3300 (NH), 2545 (SH) 1671 (NCO) cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.51, 11.81 (2s, 1H each, 2NH), 8.21–7.63 (m, 4H, ArH), 4.25 (s, 2H, CH_2), 3.64 (s, 1H, SH) ppm. MS: *m/z* (%) = 420 (M^+ + 1, 30).
4a	IR : ν = 3225 (NH), cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.65, (s, 1H, NH), 8.25–7.44 (m, 5H, ArH), 4.15 (s, 2H, CH_2) ppm.
4b	IR : ν = 3220 (NH), cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 11.92 (s, 1H, NH), 8.46–7.29 (m, 4H, ArH), 4.15 (s, 2H, CH_2), 2.41 (s, 3H, CH_3) ppm. MS: *m/z* (%) = 370 (M^+, 27).
4c	IR : ν = 3220 (NH), cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.22 (s, 1H, NH), 8.24–7.44 (m, 4H, ArH), 4.25 (s, 2H, CH_2) ppm. MS: *m/z* (%) = 390 (M^+, 9.8).
4d	IR : ν = 3125 (NH), cm^{-1}. ^{1}HNMR (DMSO-d_6): δ = 12.43 (s, 1H, NH), 8.11–7.45 (m, 4H, ArH), 4.18 (s, 2H, CH_2) ppm.

TABLE III Antimicrobial Activity Data of the Prepared Compounds (MIC in μg/mL)

Compound	*S. aureus*	E. Coli	*C. albicans*
2a	> 200	100	100
2c	100	100	50
3a	50	50	25
3c	50	50	50
4a	100	>200	>200
6	> 200	100	100
Ampicillin	12.5	25	—
Clotrimazole	—	—	12.5

General Procedure for the Preparation of 4-aroylamino-3-methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-1,2,4-triazole-5-thiols (3a–d)

A mixture of **1** (0.5 g, 1.85 mmol) and the suitable aromatic acid chloride (0.3 g, 1.85 mmol) in pyridine (2 mL) was heated under reflux at 100°C for 1 h. After attaining room temperature, ice-water (20 mL) was added to the reaction mixture and then extracted with chloroform. The chloroform extract was washed with aqueous sodium bicarbonate solution and water, dried and evaporated. The collected residue was crystallized from ethanol. The physical constants and spectral data of compounds (**3a**–**d**) are given in Tables I and II.

General Procedure for the Preparation of 6-aryl-3-methylthio{7H-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (4a–d)

Method (A)

A solution of the respective **2a**–**d** (0.5 g) in ethanol (15 mL) was treated with 5% palladium-on-charcoal (0.2 g) and heated under reflux for 2 h. The catalyst was filtered off and the filtrate evaporated. The obtained product was crystallized from ethanol.

Method (B)

A mixture the appropriate **3a**–**d** (0.5 g) and phosphorus oxychloride (10 mL) was heated under reflux for 1 h. and then allowed to cool at room temperature. The reaction mixture was poured onto a diluted aqueous solution of sodium bicarbonate. The precipitated solid product was filtered and washed with cold water. The collected solid was dried and crystallized from ethanol.

Method (C)

A mixture of aminothiol **1** (0.5 g, 1.85 mmol), and suitable aromatic carboxylic acid (0.23 g, 1.85 mmol) solubilized in phosphorus oxychloride (15 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured onto cold sodium bicarbonate solution. The resulting solid product that formed filtered off, washed with water and crystallized from ethanol.

The physical constants and spectral data of compounds (**4a**–**d**) are given in Tables I and II.

Synthesis of Compounds 5–8—General Procedure

A mixture of compound **1** (0.5 g, 1.85 mmol) and the appropriate reagents, namely: chloroacetone (0.17 g, 1.85 mmol), pyruvic acid (0.16 g, 1.85 mmol), benzoylformic acid (0.28 g, 1.85 mmol), and benzoin (0.39 g, 1.85 mmol) in phosphorus oxychloride (10 mL) was refluxed for 2–3 h, slowly quenched onto crushed ice with stirring and it was neutralized with solid sodium bicarbonate. The solid which separated was filtered and crystallized from ethanol.

The characterization data of these compounds follow.

6-Methyl-7H-3-methylthio{7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl}-1,2,4-triazolo[3,4-bi b]-1,3,4-thiadiazine (5)

Yield: 58%; m.p. 220–221°C; : $\nu = 3250$ (NH)cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 12.60$ (s, 1H, NH), 4.15, 4.05 (2s, 2H each, $2CH_2$), 2.30 (s, 3H, CH_3) ppm. MS: m/z (%) = 309 ($M^+ + 1$, 28).

Anal. calcd. for $C_8H_8N_{10}S_2$: C, 31.17; H, 2.60; N, 45.46%. Found : C, 31.51; H, 3.09; N, 45.91%.

6-Methyl-3-methylthio{7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl}-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazin-7-one (6)

Yield: 65%; m.p. 195–197°C; IR : $\nu = 3230$ (NH), 1730 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6) : $\delta = 12.55$ (s, 1H, NH), 4.10 (s, 2H, CH_2), 2.15 (s, 3H, CH_3) ppm.

Anal. calcd. for $C_8H_6N_{10}OS_2$: C, 29.81; H, 1.86; N, 43.48%. Found: C, 30.22; H, 1.52; N, 43.63% .

3-Methylthio{7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl}-6-phenyl-1,2,4-triazolo [3,4-bi b]-1,3,4-thiadiazin-7-one (7)

Yield: 71%; m.p. 180–182°C; IR : ν =3235 (NH), 1740 (CO) cm^{-1}. MS: m/z (%) = 385 ($M^+ + 1$, 32).

Anal. Calcd. For $C_{13}H_8N_{10}OS_2$: C, 40.63; H, 2.08; N, 36.46%. Found: C, 40.13; H, 2.52; N, 36.13% .

6,7-Diphenyl-3-methylthio{7H-1,2,4-triazolo[1,5-d]tetrazol-6-yl}-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine (8)

Yield: 60%; m.p. 224–226°C; IR : ν=3200 (NH) cm^{-1}. ^1H NMR (DMSO-d_6) : $\delta = 12.10$ (s, 1H, NH), 8.30–7.55 (m, 10H, ArH), 7.25 (s, 1H, CH); 4.25 (s, 2H, CH_2) ppm. MS: m/z (%) 446 (M^+ , 16).

Anal. calcd. for $C_{19}H_{14}N_{10}S_2$: C, 51.12; H, 3.14; N, 31.39%. Found: C, 51.22; H, 3.44; N, 31.83% .

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